Major Histocompatibility Complex and Cell Cooperation[1]

OLLI VAINIO,[2] PAAVO TOIVANEN, and AULI TOIVANEN

Department of Medical Microbiology and Medicine, Turku University, SF-20520 Turku, Finland

and

Basel Institute for Immunology, Grenzacherstrasse 487 CH-4005 Basel, Switzerland

(Received for publication January 7, 1987)

ABSTRACT We have studied the role of major histocompatibility antigens on cell cooperation in the immune response of the chicken. In the 1970's, shortly after the initial discoveries in the mouse, we demonstrated that the T cell-B cell interaction is major histocompatibility complex (MHC)-dependent in the chicken and requires at least one haplotype identity between the collaborating cells. Later, by using MHC-congenic and MHC-recombinant lines, we demonstrated that the T-B cell interaction in antibody response is MHC-restricted, and more precisely, Class II MHC-antigen-restricted. Furthermore, we proved that T-B cell cooperation in splenic germinal center formation is likewise class II MHC antigen-restricted.

Recently, we have focused our studies on MHC antigen identity requirements during antigen presentation by macrophages to T cells. In these studies, Class II antigens were found to serve as restriction elements in antigen recognition by T cells. Cytotoxic T cells of the chicken have been shown to be MHC-restricted in their function. Whether Class I or Class II MHC antigens serve as restriction molecules has not yet been determined. In conclusion, it is obvious that the function of the avian immune response is controlled by the polymorphic MHC gene products in the same way as that in the mammalian species.
(*Key words:* antigen-presenting cell, cell cooperation, major histocompatibility complex, antigen restriction)

1987 Poultry Science 66:795–801

INTRODUCTION

The chicken major histocompatibility complex (MHC) was described almost 40 years ago by Briles and his coworkers as one of the major blood group systems, the *B* blood group (Briles *et al.*, 1950). Later, Schierman, and Nordskog (1961) demonstrated that skin graft rejection was determined by incompatibilities associated with this particular blood group system, thus directly proving that MHC antigens were encoded in the *B* locus. In 1974, shortly after the initial discoveries in the mouse made by Kindred and Shreffler (1972) and Katz and his coworkers (1973), we demonstrated that thymal (T) cell and bursal (B) cell collaboration in the chicken is dependent on MHC compatibility (Toivanen *et al.*, 1974a,b).

However, in spite of this early description of the chicken MHC and of the requirement of histocompatibility for T and B cell collaboration, knowledge of the role of MHC in the regulation of an immune response in chickens lags far behind what is known for several mammalian species. One of the major reasons for this has been the scarcity of MHC recombinant and congenic chicken strains. Recently, fully analyzed and progeny-tested recombinants, as well as strains of chickens that behave as if they had undergone a recombinational event in the past, have been found and used in immunogenetic studies. In this review, we will briefly discuss the current knowledge of the role of MHC antigens in cell cooperation during an immune response.

MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS AND RECOMBINANT LINES OF CHICKENS

The chicken MHC consists of Class I and Class II genes as in such mammalian species as the mouse and man (Pink *et al.*, 1977; Crone and Simonsen, 1986). Chicken Class I antigens are called B-F and Class II antigens B-L. Genes coding for Factor B (Class III genes) have not

[1]Original studies were financially supported by the Sigrid Jusélius Foundation, the Finnish Cancer Union, Turku University Foundation and the Paulo Foundation. Basel Institute for Immunology was founded and is entirely supported by F. Hoffmann-La Roche, Ltd., Co., Basel, Switzerland.

[2]Address correspondence to the Basel Institute for Immunology.

been found within the chicken MHC (Koch, 1986). The chicken does have Class IV genes and antigens; these have been identified so far only in avian species with nucleated erythrocytes. Only in the frog has a potential homologous antigen been found (Flajnik *et al.*, 1985).

Class I or B-F antigens resemble the mammalian Class I antigens. They are found on most nucleated cells; in the chicken this includes also the erythrocytes. The molecular structure is very similar to that in the mammalian species, consisting of two noncovalently bound glycoproteins of relative molecular mass (M_r) in the reduced form of 40,000 to 43,000 and 11,000 to 12,000. The heavy chain is anchored into the cell membrane and is associated with the β_2-microglobulin light chain that presumably is not encoded within the MHC. Both of the chains show a great homology in amino acid sequences to the corresponding mammalian chains.

Class II antigens or B-L antigens of the chicken are also similar to those of mammalian species being found on the surface of B lymphocytes, monocytes, macrophages, and stimulated T cells. They are composed of two noncovalently linked glycoproteins of M_r of about 30,000 to 32,000 (α-chain) and 27,000 to 30,000 (β-chain). In Class I antigens, the polymorphism occurs only in the heavy chain; in Class II antigens, the smaller β-chain is the more polymorphic one.

About 30 different alleles are found in both Class I and II loci. This figure applies also to the products of Class IV genes. Biochemical evidence has been presented to suggest that at least two different subloci exist for both Class I and Class II genes (Crone *et al.*, 1981, 1985). This evidence is based on studies with sequential precipitation of the cell surface molecules and remains to be proven by DNA sequencing of these genes.

Class IV, or B-G, antigens represent MHC antigens found only in the avian species. They are also found on the erythrocyte precursors (Longenecker and Mosmann, 1980). The molecular appearance of these antigens is not known to the same extent as that of the Class I or Class II antigens. Most probably they are composed of nonglycosylated proteins of M_r of about 48,000 (Miller *et al.*, 1984). It remains to be seen how closely they are related to the blood group antigens A in the horse and M in the cattle, which are also known to be coded by genes in the same chromosome as the MHC.

Avian MHC genes are located on one of the small acrocentric chromosomes of the size range ~16 (Bloom and Bacon, 1985). The order of subloci in the chromosome has been suggested to be: *B-L, B-F* and *B-G* (Crone and Simonsen, 1986). The location of the centromere is not known. Calculated genetic distance between Class I and Class IV genes is about .04 cM; this figure is based on the recombination frequency between these two loci (Hála *et al.*, 1976; Koch *et al.*, 1983). All the published and well characterised recombinants in the chicken MHC have occurred between Class I and Class IV genes. In spite of more than 6,000 informative typings analyzed from different matings, no crossing-over has been found to occur between Class I and Class II genes; this suggests that they are more closely linked to each other than to Class IV genes.

All available findings indicate that crossing-over in the chicken MHC is a considerably more rare event than in the mammalian MHC; this suggests that the chicken MHC is probably a short chromosomal region and does not contain the same kind of hot spots for recombination as found in the murine MHC (Steinmetz *et al.*, 1986). This creates a very strong linkage disequilibrium in the chicken MHC, and further leads to the occurrence of so-called standard haplotypes (in a standard haplotype, a particular *B-F* allele is invariably associated with a *B-L* allele of the same haplotype (Simonsen *et al.*, 1982).

The Innsbruck MHC workshop in 1981 recommended that a recombinant haplotype should be designated with a letter *B* followed by the number of the *B-F* allele present in the new haplotype, and further followed by a superscript *r* and a number 1 for the first recombinant haplotype carrying this particular allele, 2 for the second, etc. (Briles *et al.*, 1982). Thus B^{12r1} was the first recombinant carrying *B-F* allele *12*. This and the many other recombinant haplotypes described in several laboratories around the world are so called man-made or laboratory recombinants. In addition, spontaneous recombinants also exist. For instance, the Strains *CHA* and *CB* (B^{12}) share similar B-L antigens with the Strain *H.B*^{19} (B^{19}). Class II antigens of these two haplotypes appear serologically identical, since complete crosswise absorption can be obtained (Simonsen *et al.*, 1982). Likewise, there is a lack of B-L specific aloantibody formation after reciprocal cross immunizations. In spite of this serological identity, there is low mutual mixed lymphocyte reactivity (MLR). Here one

must remember that as in mammalian species, differences with Class I antigens contribute to some extent to that reaction. Studies at the DNA level have revealed difference in restriction fragment length polymorphism (RFLP) analysis between the Class II genes of *CB* and *H.9*[19] strains (C. Auffray, personal communication). However, this does not necessarily indicate that a difference also exists at the protein level. Taken generally, in spite of the studies started in several laboratories, very little information is available at the DNA level regarding the chicken MHC.

Perhaps the most interesting among the similarities of MHC antigens in different strains is that found in birds in a small flock of red jungle fowl at the Copenhagen Zoological Garden. Analysis of the two haplotypes, described as B^{w3} and B^{w4} and derived from a heterogenous rooster, demonstrated that B-L^{w3} and B-L^{w4} antigens were different while B-F and B-G antigens were similar and possibly identical (Crone and Simonsen, 1986). Crone and Simonsen introduced this recombinant haplotype to White Leghorn chickens and as a result, a useful recombinant pair of White Leghorn chickens exists, with different B-L but supposedly identical B-F and B-G antigens.

ROLE OF MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS IN THYMUS-DERIVED AND BURSAL-DERIVED CELL COOPERATION

Recombinant strains that we have used in our immunogenetic studies and that are kept at Turku University are listed in Table 1. In the studies on MHC restriction of T and B cell cooperation, we have extensively used the cyclophosphamide (Cy) model (Figure 1), in which newly hatched chickens are treated with this cytotoxic drug. The treatment results in a life-long inability to form specific antibodies and in B cell depletion. It is possible to confer specific antibody formation ability on the Cy-treated birds in the newly hatched period with bursal stem cells taken from age-matched normal donors (Toivanen and Toivanen, 1973). The result is a chimera, with donor-derived B cells and host-derived T cells, which gives an opportunity to study collaborative functions of the different cell types *in vivo*. Even transplantation of allogeneic bursal cells results in an immunological chimera tolerant to donor line skin grafts (Lehtonen *et al.*, 1985). The chimera is morphologically fully reconstituted with a normal number of B cells in the different lymphoid organs. In the presence of full identity at the three MHC subloci, the antibody functions become reconstituted. However, if lacking the identity, only those antibody functions become reconstituted that do not require collaboration between T and B cells, e.g., antibody formation against *Brucella abortus*, a thymus independent antigen (Toivanen *et al.*, 1974a,b).

In further studies, we also formally proved that only MHC antigens play a role in controlling T-B cell cooperation. Using the Cy-model of B-cell reconstitution and a pair of MHC-congenic chicken [CC (B^4) and CB (B^{12}) chickens from Praguel], we have demonstrated that only MHC genes and not the genetic background affect successful T-B cell cooperation (Table 2). Likewise, compatibility at the *B-G* locus is irrelevant for the functional reconstitution of the Cy-treated recipients (Vainio *et al.*, 1984). This was demonstrated using H.B^{21r3} recombinant chickens sharing B-G antigens of the B^{15} haplotype. Finally, using as donors and recipients a pair of chickens with standard haplotypes that behave as if they had undergone a recombinational event in the past, we have been able to dissect the genetic requirements for T-B cell cooperation in the chicken. The CB (or CHA) chickens with haplotype B^{12} and H.B^{19} chickens (B^{19}) have very similar or identical B-L antigens whereas their B-F and B-G antigens are clearly different. With this pair of 'spontaneous' recombinants, we discovered that B-L antigen identity between the bursa cell donors and the recipients is necessary and also sufficient for a normal T-B cell collaboration during immune response (Table 3).

In our earlier studies, we also found that germinal center formation in the recipient spleen requires MHC identity between transplanted bursa cells and the recipient (Toivanen and Toivanen, 1977). In the connection of the cell

TABLE 1. *Recombinant lines used to study major histocompatibility complex restriction in the chicken*

Line	*B* complex		
	L (Class II)	*F* (Class I)	*G* (Class IV)
H.B^{15r1}	15	15	21
H.B^{21r3}	21	21	15
CHA or CB	12	12	2
H.B^{19}	12	19	19
H.B^{w3}	*w*3	*w*3	*w*3
H.B^{w4}	*w*4	*w*3	*w*3

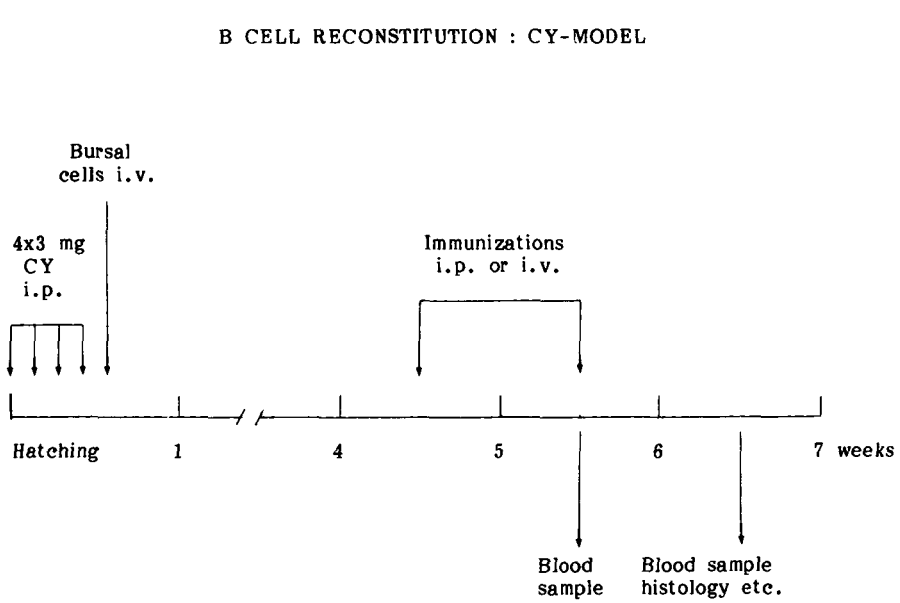

FIG. 1. In the cyclophosphamide (Cy) model for bursal (B) cell reconstitution, newly hatched chickens are injected with 3 mg of Cy i.p. for 4 consecutive days starting on the day of hatching. This treatment renders them hypogammaglobulinemic and B cell deficient. One day after the last Cy injection chickens are reconstituted with 4-day-old normal B cells containing B stem cells. In order to test functional reconstitution of the B cell compartment, recipient chickens are injected either i.p. or i.v. with antigens at 4.5 and 5.5 weeks of age. Five to 7 days after the booster, histological samples are prepared from bursa and spleen to analyze morphological reconstitution. Specific antibodies in serum samples and plaque-forming cells in the spleen are also analyzed.

transfer studies with MHC recombinant chickens, the germinal center formation was proven to be MHC-restricted in the same way as antibody formation, requiring identity at the *B-L* locus (Vainio *et al.*, 1984). Class I and B-G antigen identity is not sufficient for successful T-B cell interaction that is needed for germinal center formation (Table 4). In conclusion, it is evident that, as in mammals, avian T-B cell interactions are controlled by Class II gene products that serve as restriction elements.

ROLE OF MAJOR HISTOCOMPATIBILITY COMPLEX ANTIGENS IN THYMUS-DERIVED CELL-MACROPHAGE INTERACTION

In another series of experiments, we have studied MHC restriction of the antigen-specific proliferation of chicken T cells (Vainio *et al.*, unpublished results). For this purpose, adult chickens were primed with keyhole limpet hemocyanin (KLH); peripheral blood lymphocytes were collected, cultured *in vitro* with KLH and further propagated with interleukin-2 (IL2).

TABLE 2. *Thymal-bursal cell cooperation is controlled by the major histocompatibility complex (MHC) antigens*[1]

Line		MHC Identity			Log_2 titer against		Anti-SRBC PFC/10^6 spleen cells	
Donor	Recipient	*B-L*	*B-F*	*B-G*	SRBC	*Brucella*	IgM	IgG
CB	CC	–	–	–	.6	2.8	<8	<8
CB	CB	+	+	+	9.3	3.5	2,450	5,530
	CC				.3	.2	<8	<8
	CB				.2	0	<8	<8

[1]The 2 × 10^7 4-day-old bursal cells were transplanted i.v. into age-matched cyclophosphamide-treated recipients. Four weeks later recipients were immunized twice i.v. at 1-week intervals with sheep red blood cell (SRBC) and killed *Brucella abortus* bacteria. Five days after the second immunication antibody titers in the serum (expressed as mean log_2 titer) were analyzed and the number of anti-SRBC plaque forming cells (PFC) in the spleen was counted. Data from Vainio *et al.* (1984).

TABLE 3. *Class II antigens (B-L) restrict thymal and bursal cell cooperation*[1]

Line		MHC[2] identity			Log_2 titer against		Anti-SRBC PFC/10^6 spleen cells
Donor	Recipient	*B-L*	*B-F*	*B-G*	SRBC	*Brucella*	
CB	CB	+	+	+	9.3	3.5	5,530
CB	H.B[19]	+	−	−	7.6	3.8	3,700
CB	H.B[14]	−	−	−	0	2.9	<8
H.B[19]	CB	+	−	−	5.8	3.0	4,580
	H.B[19]				0	0	<8

[1]The 2 X 10^7 4-day-old bursal cells were transplanted i.v. into age-matched cyclophosphamide-treated recipients. Four weeks later recipients were immunized twice i.v. at 1-week interval with sheep red blood cell (SRBC) and killed *Brucella abortus* bacteria. Five days after the second immunization antibody titers in the serum (expressed as mean log_2 titer) were analyzed and the number of anti-SRBC plaque-forming cells (PFC) in the spleen was counted. Data from Vainio *et al.* (1984).

[2]MHC - Major histocompatibility complex.

TABLE 4. *Class II antigens (B-L) restrict germinal center formation in the spleen*[1]

Line		MHC[2] identity			Germinal
Donor	Recipient	*B-L*	*B-F*	*B-G*	centers
CB	CB	+	+	+	58
CB	CC	−	−	−	0
H.B[15]	H.B[21 r3]	−	−	+	2
H.B[21]	H.B[21 r3]	+	+	−	56
CB	H.B[19]	+	−	−	62

[1]The 2 X 10^7 4-day-old bursal cells were transplanted i.v. into age-matched cyclophosphamide-treated recipients. Number of germinal centers is expressed as a mean number per cross section of the spleen. Data from Vainio *et al.* (1984).

[2]MHC = Major histocompatibility complex.

The resulting blast cells were grown together on microtiter plates with antigen-pulsed peripheral blood adherent cells. Both KLH and bovine serum albumin (BSA) were used as the antigens in *in vitro* tests and concanavalin A (Con A) served as a nonspecific mitogen control. Con A stimulation resulted in a clear proliferation of the KLH blasts, BSA resulted in no proliferation, whereas KLH-pulsed adherent cells induced a vigorous proliferation of the IL2-propagated KLH blasts. With this experimental set-up, we were able to show that B-G antigens are irrelevant for antigen presentation by adherent cells to primed T cells (Table 5). Only in the presence of identity at *B-L* and *B-F* loci, was a vigorous cell proliferation produced. Finally, use of CHA and H.B[19] strains sharing the iden-

TABLE 5. *Class II antigens (B-L) restrict antigen-specific thymal (T) cell proliferation in the chicken*[1]

Responding T cells	Antigen-pulsed macrophages	MHC[2] identity			Proliferative response (cpm) in vitro to:	
		B-L	*B-F*	*B-G*	KLH[2] (100 μg/ml)	BSA[2] (100 μg/ml)
H.B[19]	H.B[19]	+	+	+	8,400	640
CHA	H.B[19]	+	−	−	10,910	730
H.B[2]	H.B[19]	−	−	−	1,200	640
CHA	CHA	+	+	+	15,810	640
H.B[19]	CHA	+	−	−	13,670	1,800
H.B[2]	CHA	−	−	+	1,810	1,300

[1]The 2 X 10^5 IL2 propagated keyhole limpet hemocyanin (KLH) blasts were cultred in 200 μl volume at 40 C for three days on KLH-pulsed peripheral blood adherent cells. Proliferation was measured by the uptake of ^{125}I-5-iodo2′deoxyuridine precursor and results are expressed as mean counts per minute from triplicate cultures.

[2]MHC = Major histocompatibility complex, KLH = keyhole limpet hemocyamin, BSA = bovine serium albumin.

TABLE 6. *Inhibition of keyhole limpet hemocyanin (KLH)-specific thymal cell proliferative response by a monoclonal antibody (21-1A6) against chicken Class II major histocompatibility complex antigen*[1]

Antibody dilution	Proliferative response (cpm) to KLH (100 μg/ml)
Control antibody (1:100)	16,870 ± 2,730
1:100	1,460 ± 820
1:400	5,720 ± 710
1:1,600	9,280 ± 810
1:6,400	10,550 ± 70
1:25,600	16,920 ± 1,460

[1] Indicated concentration of the antibody (ascitic fluid) was added in the beginning of the culture. The 7×10^5 peripheral blood lymphocytes (PBL) from a KLH-primed animal were cultured in 200 μl volume with KLH and the antibody at 40 C for 4 days. Proliferation was measured by the uptake of ^{125}I-5-iodo-2′deoxyuridine precursor and results are expressed as mean counts per minute ± SD from triplicate cultures.

tical Class II antigens revealed that Class II or B-L antigen identity alone is sufficient to allow cooperation between antigen-presenting macrophages and T cells. Final proof for the role of Class II antigens in this function came from experiments where antigen presentation by macrophages could be blocked by a monoclonal antibody directed against a monomorphic B-L determinant (Table 6; Vainio *et al.*, unpublished results).

SUMMARY

In summarizing the MHC restricted lymphocyte functions in the chicken, it becomes apparent that the same rules apply for the chicken as for the mouse and man. Class II antigens restrict T and B cell cooperation allowing antibody production and germinal center formation. They also restrict antigen presentation to T cells by macrophages in antigen-specific T cell responses. On the other hand, cytotoxic T cell responses are known to be restricted by the MHC, but the identity of the restricting sublocus has not yet been determined (Maccubbin and Schierman, 1986); this issue will be dealt with in more detail in the subsequent paper by Schierman and Collins.

Finally, it is worth emphasizing the similarities between the chicken MHC and the corresponding genetic structures in other species. Chicken Class I and Class II genes appear both in structure and function similar to those in the mouse and man. That MHC genes are so closely related in species that diverged from each other more than 200 million years ago is indicative of extensive genetic preservation during evolution. Dissimilarities include lack of Factor B genes in the chicken and the occurrence of chicken Class IV genes and antigens not found in mammalian species.

REFERENCES

Bloom, S. E., and L. D. Bacon, 1985. Linkage of the major histocompatibility (*B*) complex and the nucleolar organizer in the chicken. Assignment to a microchromosome. J. Hered. 76:146–154.

Briles, W. E., W. H. McGibbon, and M. R. Irwin, 1950. On multiple alleles affecting cellular antigens in the chicken. Genetics 35:633–652.

Briles, W. E., N. Bumstead, D. L. Ewert, D. G. Gilmour, J. Gogusev, K. Hála, C. Koch, B. M. Longenecker, A. W. Nordskog, J.R.L. Pink, L. W. Schierman, M. Simonsen, A. Toivanen, P. Toivanen, O. Vainio, and G. Wick, 1982. Nomenclature for chicken major histocompatibility (*B*) complex. Immunogenetics 15:441–447.

Crone, M., J. Jensenius, and C. Koch, 1981. Evidence for two populations of B-L (Ia-like) molecules encoded by the chicken MHC. Immunogenetics 13:381–391.

Crone, M., and M. Simonsen, 1987. Avian major histocompatibility complex. Pages 25–41 *in:* Avian Immunology; Basis and Practice. Vol. II. Ch. 3. A. Toivanen and P. Toivanen, ed. CRC Press, Boca Raton, FL.

Crone, M., M. Simonsen, K. Skjodt, K. Linnet, and L. Olsson, 1985. Mouse monoclonal antibodies to class I and class II antigens of the chicken MHC. Evidence for at least two class I products of the B complex. Immunogenetics, 21:181–187.

Flajnik, M. F., J. F. Kaufman, and L. Du Pasquier, 1985. Studies on the Xenopus major histocompatibility complex. Dev. Comp. Immunol. 9:777–781.

Hála, K., M. Vilhelmová, and J. Hartmanová, 1976. Probable crossing-over in the B blood group system of chickens. Immunogenetics 3:97–103.

Katz, D. H., T. Hamaoka, and B. Benacerraf, 1973. Cell interactions between histoincompatible T and B lymphocytes. II. Failure of physiological cooperative interactions between histoincompatible T and B lymphocytes from allogeneic donor strains in humoral response to hapten-protein conjugates. J. Exp. Med. 137:1405–1418.

Kindred, B., and D. C. Shreffler, 1972. H-2 dependence of cooperation between T and B cells in vivo. J. Immunol. 109:940–943.

Koch, C., 1987. Complement system in avian species. Pages 43–55 *In:* Avian immunology: Basis and Practice, Vol. II, Ch. 4. A. Toivanen and P. Toivanen, ed. CRC Press, Boca Raton, FL.

Koch, C., K. Skjødt, A. Toivanen, and P. Toivanen, 1983. New recombinants within the MHC (B complex) of the chicken. Tissue Antigens 21:129–137.

Lehtonen, L., O. Vainio, E. Eerola, and P. Toivanen, 1985.

Lymphoid cell chimerism and transplantation tolerance induced by bursal and postbursal cells. Transplantation 40:398–405.

Longenecker, B. M., and T. R. Mosmann, 1980. Restricted expression of an MHC allo-antigen in cells of the erythroid series: a specific marker for erythroid differentiation. J. Supramol. Struct. 13:395–400.

Maccubbin, D. L., and L. W. Schierman, 1986. MHC-restricted cytotoxic response of chicken T cells: expression, augmentation, and clonal characterization. J. Immunol. 136:12–16.

Miller, M. M., R. Goto, and H. Abplanalp, 1984. Analysis of the B-G antigens of the chicken MHC by two-dimensional gel electrophoresis. Immunogenetics 20:373–385.

Pink, J.R.L., W. Droege, K. Hála, V. Miggiano, and A. Ziegler, 1977. A three locus model for the chicken major histocompatibility complex. Immunogenetics 5:203–216.

Schierman, L. W., and A. W. Nordskog, 1961. Relationship of blood type to histocompatibility in chickens. Science 134:1008.

Simonsen, M., M. Crone, C. Koch, and K. Hála. 1982. The MHC haplotypes of the chicken. Immunogenetics 16:513–532.

Steinmetz, M., D. Stephan, and K. Fischer Lindahl, 1986. Gene organization and recombinational hotspots in the murine major histocompatibility complex. Cell 44:895–904.

Toivanen, A., and P. Toivanen, 1977. Histocompatibility requirements for cellular cooperation in the chicken: generation of germinal centers. J. Immunol. 118:431–436.

Toivanen, P., and A. Toivanen, 1973. Bursal and postbursal stem cells in chicken. Functional characteristics. Eur. J. Immunol. 3:585–595.

Toivanen, P., A. Toivanen, and T. Sorvari, 1974a. Incomplete restoration of the bursa-dependent immune system after transplantation of allogeneic stem cells into immunodeficient chicks. Proc. Natl. Acad. Sci. 71:957–961.

Toivanen, P., A. Toivanen, and O. Vainio, 1974b. Complete restoration of bursa-dependent immune system after transplantation of semiallogeneic stem cells into immunodeficient chicks. J. Exp. Med. 139:1344–1349.

Vainio, O., C. Koch, and A. Toivanen, 1984. B-L antigens (class II) of the chicken major histocompatibility complex control T-B cell interaction. Immunogenetics 19:131–140.